Regular Review

Management of septic shock

JD Edwards

There have been important advances in the resuscitation of patients in septic shock in recent years. Survival can be improved by earlier recognition and therefore eradication of the sepsis combined with logical supportive measures. As with any acutely ill patient consultation with intensive care unit staff may be useful. Consultation with the intensive care unit does not necessarily imply the need for admission and mechanical ventilation; helpful advice may be forthcoming. Equally, referral to the intensive care unit does not mean an admission of failure but merely a recognition that additional skills and technical facilities are necessary for the patient's survival.

The management of septic shock highlights many of the difficulties encountered in the care of critically ill patients. Septic shock patients are often referred to the intensive care unit in a moribund, if not morbid condition. This is not because of lack of medical attention but is because of lack of recognition of the syndrome and the dire state of the patient. This is due to unfamiliarity with the syndrome. Although identical clinical and haemodynamic features may be seen in Gram positive and Gram negative shock, in clinical practice Gram negative shock is much more common, especially in patients after surgery. The sources are the peritoneum, the large bowel, and the biliary and genitourinary tracts. The index of suspicion in patients who collapse after operation or instrumentation of these areas should be high. Although people concerned in the management of critically ill patients find this state of affairs difficult to understand, frustration must be tempered by the realisation that, although this is virtually a daily clinical problem on the intensive care unit, it is an infrequent and sometimes unique complication in a large population at risk for the (usually) junior doctor initially confronted with the patient on the ward. For instance, although septic shock is a rare complication of operations on the urinary tract, when it occurs it is rapid and dramatic.¹

The situation is made worse by stylised preconceptions of the clinical presentation of septic shock. The classic picture of high fever, flushed face, tachycardia, bounding pulse, an obvious clinical site of infection, and neutrophil leucocytosis is easy to recognise but occurs infrequently.² Indeed, in any patient in shock the cardiac output cannot be estimated by clinical assessment of the skin temperature or even the most accurate measurements of the difference between the core and peripheral temperatures.³ Compounding the difficulties in management is that, unlike the classic experimental haemorrhagic model of shock taught to medical students—progressive tachycardia and hypotension occurring over the course of the experiment⁴—

Box A

Supportive aspects of management of septic shock

Aim

- To reduce mortality

Achieved by

- Early recognition
- Supportive measures
- Attending senior doctor/intensive care unit consultation

septic shock patients show a gradual and relatively trivial deterioration in blood pressure followed by rapid circulatory and respiratory failure and collapse.⁵ Septic shock often mimics other illnesses. One of its main physiological and clinical manifestations is acute respiratory distress,^{6,7} which may confuse the attending doctor and stop him or her giving appropriate volume therapy or, more disastrously, lead to the use of diuretics. In addition, improvements in surgical and anaesthetic techniques have so reduced the incidence of the syndrome or ameliorated its effects that it may not be recognised until too late.

Management of septic shock may be divided into (a) general supportive care and (b) specific measures aimed at identifying and removing the septic source. These second measures have been extensively reviewed. In this article, therefore, I concentrate entirely on supportive aspects of management (box A).

Management before admission to intensive care unit INITIAL ASSESSMENT AND RESUSCITATION

Initial assessment must include recording the usual vital signs. I cannot overemphasise the importance of tachypnoea as a presenting clinical feature or the value of regular assessment of respiratory rate and pattern during treatment. The threshold for endotracheal intubation and mechanical ventilation should be low. How can we distinguish a patient who needs the full range of intensive care facilities from the many patients who respond to adequate increases in inspired oxygen concentration and volume loading? In addition to the usual investigations in acutely ill patients (including full blood count; microbiological studies, including blood culture; electrocardiography; chest x ray examination; and urea and electrolyte, and plasma glucose, and serum amylase estimations) there are two tests which have enormous value when results are interpreted skilfully. These are arterial blood gas values and blood lactate concentrations.

The usual changes in arterial blood gas values in a patient with septic shock breathing room air are

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Box B

Typical blood gas values and respiration in patient with septic shock

Patient breathing air (fractional inspired oxygen 0.21)

Hydrogen ion concentration	pH 7.52
Arterial carbon dioxide pressure	3.4 kPa
Arterial oxygen pressure	9.2 kPa
Lactate	1.7 mmol/l
Respiratory rate	42/min

Patient breathing oxygen (fractional inspired oxygen 0.6)

Hydrogen ion concentration	pH 7.49
Arterial carbon dioxide pressure	4.2 kPa
Arterial oxygen pressure	27.0 kPa
Lactate	0.6 mmol/l
Respiratory rate	30/min

arterial hypoxaemia, hypocarbia, and mild alkalosis (box B). If such a patient had a satisfactory response to an increase in inspired oxygen concentration—that is, as shown by the arterial oxygen tension returning to normal, an improvement in respiratory rate and pattern, and the blood pressure and urine output restored to normal—there would be no cause for concern. Let us, however, consider a patient in whom hypoxaemia persists despite a high concentration of inspired oxygen and there is the ominous combination of metabolic acidosis, an increased blood lactate concentration, and a normal arterial partial pressure of carbon dioxide (box C). Whatever the clinical impression such a patient is near to death. Other important clues to the gravity of the condition are the presence of septic encephalopathy (which presents as confusion or drowsiness) and—in contrast with other forms of shock—relative bradycardia.

HAEMODYNAMIC CHANGES

The haemodynamic changes in septic shock consist of reduced left ventricular pre-load, myocardial depression, and peripheral vasodilatation.⁸ In the pulmonary circulation there may be preservation of vascular tone and relative pulmonary hypertension, exacerbated by alveolar hypoxia. The hypovolaemia may be due to absolute volume depletion as a result of vomiting, diarrhoea, sweating, hyperventilation (often made worse by use of inadequately humidified oxygen), ileus, and localised extravasation of fluid into inflamed tissues and generalised loss owing to increased capillary permeability. In addition, there may be dilatation of the systemic venous system with peripheral pooling of blood, producing relative hypovolaemia. These features, which often occur together, may produce a need for apparently worryingly large amounts of fluid replacement. The exact choice of fluid is irrelevant. Despite the acrimonious debate about whether to use crystalloid or colloid, there is no evidence that either is superior. The practical points are that larger volumes of crystalloids are required and the properties of artificial colloids may not all be identical. Box D lists the components and physicochemical properties of two commonly used infusion fluids.

Fluid therapy should be guided clinically, by changes in respiratory rate, heart rate, and blood pressure. Central venous pressure monitoring may be misleading, as the reading may be high even in the presence of profound hypovolaemia.⁹ In practical terms, undertransfusion is more common than overtransfusion. An increase in circulating blood volume will lower the haemoglobin concentration by haemodilution, which should be anticipated.¹⁰ Pulse oximetry is indispensable when there are concerns over respiratory status. Even if hypotension is reversed by these measures close clinical supervision is still required and transfer to a secure monitored area desirable. Indeed, the manoeuvres described can be safely and rapidly

carried out only in a high dependency environment. If the patients respond to these basic resuscitative measures, then the term sepsis induced hypotension may be applied to distinguish them from those who require intermittent positive pressure ventilation and exogenous catecholamines.¹¹

If these measures fail or make the patient worse then referral to the intensive care unit is mandatory. The persistence of hyperlacticaemia or clinical signs of tissue hypoperfusion despite volume loading indicates that myocardial depression and systemic vasodilatation are profound. Dopamine, adrenaline, noradrenaline, and phenylephrine all function primarily as vaso-pressors in septic shock. The effects on cardiac output may be desirable but are unpredictable, and there may be a reflex fall in output in response to vasoconstriction.^{12,13} This is crucially important in view of the known dependency of oxygen consumption on oxygen delivery which occurs in septic shock.^{14,15} The effectiveness of these agents must be adequately monitored. When used inappropriately dobutamine may cause disastrous hypotension.¹⁶

Management on intensive care unit

HAEMODYNAMIC ASPECTS

Patients may be referred direct to the intensive care unit as a result of sudden, unexpected circulatory and respiratory collapse or after a period of observation and initial treatment in another part of the hospital. In either instance intubation and ventilation are implemented for the usual indications. If the patient has not received an appropriate amount of fluid, then an initial volume challenge should be initiated without any invasive monitoring. Failure to respond to volume loading may indicate that not enough fluid has been infused or that the combination of myocardial depression and systemic vasodilatation is not reversible by restoring pre-load. Under these circumstances rational treatment should be guided by invasive monitoring. Systemic and pulmonary artery catheters should be inserted immediately, especially if high concentrations of inspired oxygen are required to maintain arterial oxygen tension.

Depending on the degree of hypotension the use of blind vasopressor therapy may be indicated as a short term manoeuvre, or depending on the value of pulmonary artery occlusion pressure further fluid should be given, guided by repeated measurements of wedge pressure and cardiac output. However, an initial left ventricular stroke work index of less than 20 g.m/m² is a strong indicator that fluids alone are unlikely to reverse hypotension and that exogenous catecholamines will be required.¹⁷ In order to achieve optimal survival with a minimal incidence of multi-system organ failure a high cardiac output and thereby oxygen delivery should be maintained or achieved concomitant with reversal of hypotension. This

Box C

Typical blood gas values and respiration when hypoxaemia persists

Patient breathing air (fractional inspired oxygen 0.21)

Hydrogen ion concentration	pH 7.27
Arterial carbon dioxide pressure	4.9 kPa
Arterial oxygen pressure	7.2 kPa
Lactate	3.2 mmol/l
Respiratory rate	55/min

Patient breathing oxygen (fractional inspired oxygen 0.6)

Hydrogen ion concentration	pH 7.22
Arterial carbon dioxide pressure	4.6 kPa
Arterial oxygen pressure	8.4 kPa
Lactate	4.1 mmol/l
Respiratory rate	51/min

Box D

Composition and physicochemical properties of two common plasma substitutes

• Haemaccel (polygeline)

Presentation

3.5% Colloidal infusion solution

Composition

Polygeline	35 g/l
Cations:	
Monovalent sodium	145.0 mmol/l
Monovalent potassium	5.1 mmol/l
Divalent calcium	6.3 mmol/l
Anions:	
Monovalent chlorine	145.0 mmol/l
Trivalent phosphate	Trace
Divalent sulphate	Trace

(Isoionic equilibrium is made up by the polypeptides. There are no preservatives)

Physicochemical properties

Viscosity ratio	1.7-1.8
Dynamic viscosity (at 37°C)	1.15-1.20 kPa.s
Isoelectric point	pH 4.7±0.3
Hydrogen ion concentration	pH 7.3±0.3
Colloid osmotic pressure (at 37°C)	3.432-3.824 kPa
Gel point	< 3°C
Appearance	Straw coloured
Nitrogen equivalent of polygeline	6.3 g/l

• Gelofusine (gelatin)

Presentation

Sterile 4% (weight per volume) succinylated gelatin (modified fluid gelatin) in saline

Composition

Average molecular weight (MW)	30 000
Average molecular weight (Mn)	22 600
Gelatin (modified fluid gelatin)	40 g/l
Sodium	154.0 mmol/l
Potassium	< 0.4 mmol/l
Magnesium	< 0.4 mmol/l
Calcium	< 0.4 mmol/l
Chloride	125.0 mmol/l

Physicochemical properties

Relative viscosity (at 37°C)	1.9 kPa.s
Isoelectric point	pH 4.5±0.3
Hydrogen ion concentration	pH 7.4±0.3
Colloid osmotic pressure (at 37°C)	4.557 kPa
Gel point	0°C

approach is well validated.¹⁸⁻²⁰ It entails simultaneous use of a vasopressor and an inotropic agent. Attempts to use single agents with combined α and β effects, such as adrenaline, to achieve these aims have proved disappointing.^{13,21} The best documented regimen is noradrenaline with dobutamine. As phenylephrine is a pure α agonist, arguably it would be the most logical vasopressor to use. By monitoring treatment and avoiding excessive vasoconstriction renal function is actually improved by vasoconstriction as a result of increased renal perfusion pressure.²²

If catecholamines are used it should be appreciated that the doses required may vary from those recommended by the manufacturers and the effects at any dose may be unpredictable. Rather than using fixed rates of administration the dose should be titrated in each patient at the bedside. In one study the dose of noradrenaline varied from 0.2 to 10.0 $\mu\text{g/kg/min}$ and the dose of dobutamine varied from 22 to 200 $\mu\text{g/kg/min}$. Possible adverse reactions to catecholamines may occur at any dose. The most dangerous period is at the initiation of treatment. The cause of inadequate cardiac output response to the fall in systemic vascular resistance and increased tissue oxygen demand is generally accepted to be cardiodepressant substances, though in some patients the combination of high right atrial pressure and low systemic diastolic arterial pressure may be a potential cause of coronary hypo-

perfusion and influence the choice of vasopressor or inotrope as the initial agent. In some cases, particularly those patients with advanced peritonitis or infarcted bowel, the typical haemodynamic pattern is different.²³ They may have low levels of cardiac output and a high systemic vascular resistance, producing the clinical picture usually seen in cardiogenic shock.

VENTILATORY SUPPORT

Patients with septic shock who require intensive care, invasive monitoring, and cardiovascular support with catecholamines inevitably have a degree of acute respiratory failure, which frequently may be manifested by the full blown adult respiratory distress syndrome. Therefore, after initially securing the airway and reversing hypoxaemia simultaneous optimisation of mechanical ventilatory settings is required. The adult respiratory distress syndrome will be reviewed and is not discussed further in this article.

From the general point of view there is now widespread recognition of the need to limit the mechanical and haemodynamic effects of positive intrathoracic pressure, high intrathoracic volume, and high levels of positive end expiratory pressure. This has led increasingly to the use of tidal volumes of 10 ml/kg or less and the acceptance of moderate, asymptomatic increases in arterial carbon dioxide pressure—so called permissive hypercarbia. Positive end expiratory pressure is increasingly combined with an inspiratory time which is equal to or greater than the expiratory time—so called inverse ratio ventilation. There is evidence that this approach may be life saving in patients previously considered candidates for extracorporeal membrane oxygenation.²⁵ Of particular concern is the tendency of positive end expiratory pressure to reduce cardiac output, which will thereby lower tissue oxygen delivery and—in view of the known dependence of oxygen consumption on delivery in septic shock—may cause tissue hypoxia at the same time as increasing arterial oxygen pressure.

Oxygen transport abnormalities in septic shock

Oxygen is the most important substrate carried by the circulation. It is also the most flow dependent and, compared with its utilisation, the substrate with the most limited stores. The relation between the flow of oxygen to the tissues and its utilisation has become of great interest in the management of shock. Oxygen delivery (DO_2) is calculated as $\text{DO}_2 = \text{CI} \times \text{CaO}_2 \times 10$ (result expressed in ml/min/m^2), where CI is cardiac

Procedures for management of septic shock

index and CaO_2 is arterial content of oxygen. Oxygen consumption ($\dot{V}\text{O}_2$) is calculated as $\dot{V}\text{O}_2 = \text{CI} \times (\text{CaO}_2 - \text{C}\bar{\text{v}}\text{O}_2) \times 10$ (result expressed in ml/min/m²), where $\text{C}\bar{\text{v}}\text{O}_2$ is mixed venous content of oxygen.

In haemorrhagic or cardiogenic shock oxygen consumption is well maintained even when oxygen delivery is extremely low by increases in oxygen extraction ratio.²⁶ This may not occur in septic shock, and hyperlactacidaemia may be seen with apparently adequate perfusion pressure and normal or even high levels of cardiac output.²⁷ The mechanism of the inability to increase oxygen extraction remains speculative. The only proved solution at present is to maintain those levels of oxygen delivery shown to produce reversal of hyperlactacidaemia and optimal survival rates. This is sometimes described as maintaining "supranormal values." This is a misconception, as the normal resting oxygen delivery is around 600 ml/min/m².

From the point of view of management, interventions which reduce cardiac output such as vasopressor treatment, positive end expiratory pressure, sedatives and drugs which reduce arterial oxygen content should be monitored and any adverse effect corrected.²⁸ There has been much discussion on the ability to increase oxygen delivery to levels required to reverse hyperlactacidaemia as a prognostic sign. Plainly there will be patients with underlying cardiac disease who will not respond adequately to catecholamine infusion. The failure to respond to one catecholamine does not preclude the possibility of response to another. If there is resistance to the effects of all catecholamines, then phosphodiesterase inhibitors may help in occasional cases.

As the end organ damage in septic shock is ultimately related to the release of inflammatory mediators, recent research has investigated the possible use of specific antagonists or antibodies to these mediators. At present this is highly controversial but antibodies to circulating endotoxin, tumour necrosis factor, and, for example, interleukin 1 have been studied. Studies are under way with platelet activating factor antagonists. For the moment these drugs have not been validated and certainly are not a substitute for the basic resuscitative measures outlined above. All have been extensively reviewed.²⁹

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A DOCTOR WHO CHANGED MY PRACTICE

How not to do it

Long before the sophisticated methods of neurological investigation now routinely available, there was a noted neurologist at my London teaching hospital. He was distinguished for his ability to make accurate diagnoses in a discipline then dominated by clinical skills, a few imperfect tests, and inspired guesswork. Naturally, his outpatient clinics were popular with the students, and it was as a student that I watched a consultation that changed the whole emphasis of my career.

The patient was a concert pianist. He was not in the big league but still good enough to make a living. Now in his 50s, he had experienced some difficulties that had led to his referral. The neurologist led us through the minimal yet definite clinical signs of early Parkinson's disease. As we followed the logic of his diagnostic demonstration it was a triumph of teaching.

As the consultation ended the frightened concert pianist asked, "What is going to happen to me?" The consultant

smiled in brief insincerity and said, "I'll write to your doctor." He then signalled to the nurse for the patient to be shown out.

As we settled down to the next case I remember thinking how diagnosis was the beginning not the end for modern medicine; that the teaching hospital emphasis was not for me; and that chronic and incurable illness was the burden that I would like to share with my patients.

I did not realise then that among the glittering examples of "how to do it" of my apprenticeship years most unforgettable of all would be the occasional examples of how not to do it.—ERIC WILKES is emeritus professor of community care and general practice, University of Sheffield

We are delighted to receive submissions of up to 600 words on *A paper (or patient or book) that changed my practice, A memorable patient, The one message I would like to leave behind, or related topics.*